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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,857	02/08/2006	German Spangenberg	FREE.P-007	4572

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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	PAPER NUMBER
1638	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/552,857	SPANGENBERG ET AL.
	Examiner	Art Unit
	ANNE KUBELIK	1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *83-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *98-102* is/are allowed.

6)☒ Claim(s) *83-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 83-102 are pending.

2. The claims contain sequences drawn to an invention nonelected with traverse in the response filed 13 October 2009. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

3. The rejection of claims 65-73 and 75-82 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention is withdrawn in light of Applicant's amendment of the claims.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 83-97 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Due to Applicant's amendment of the claims, the rejection is modified from the rejection set forth in the Office action mailed 6 January 2011, as applied to claims 65-73, 75-80 and 82. Applicant's arguments filed 18 April 2011 have been fully considered but they are not persuasive.

The essential features of the claims are constructs comprising a chalcone synthase-encoding nucleic acid that has at least 95% identity to any nucleic acid encoding SEQ ID NOs:2, 4, 6, or 8, an anthocyanine reductase-encoding nucleic acid that has at least 95% identity to any nucleic acid encoding SEQ ID NO:10, and, optionally, a leucoanthocyanidine reductase-encoding nucleic acid that has at least 95% identity to any nucleic acid encoding SEQ ID NOs:12, 14 or 16.

Nucleic acids encoding SEQ ID NO:2, 10 and 14 are the elected sequences; these include SEQ ID NO:1, 9 and 13.

The specification does not describe the full scope of chalcone synthase-, anthocyanine reductase-, and leucoanthocyanidine reductase-encoding nucleic acids with 95% identity to any nucleic acid encoding SEQ ID NO:2, 10 and 14 .

Nucleic acids with 95% identity to the 1447 nucleotide long SEQ ID NO:1 would have 72 nucleotide substitutions relative to the 389 amino acid long chalcone synthase-encoding SEQ ID NO:2, and thus encompass nucleic acids encoding proteins with 72 amino acid substitutions relative to SEQ ID NO:2. These proteins would have 81.5% identity to SEQ ID NO:2.

Similarly, nucleic acids with 95% identity to the 1309 nucleotide long SEQ ID NO:9 would have 65 nucleotide substitutions relative to 338 amino acid long anthocyanine reductase-encoding SEQ ID NO:10, and thus encompass nucleic acids encoding proteins with 65 amino acid substitutions relative to SEQ ID NO:10. These proteins would have 80.7% identity to SEQ ID NO:10.

Nucleic acids with 95% identity to the 1551 nucleotide long SEQ ID NO:13 would have 77 nucleotide substitutions relative to 356 amino acid long leucoanthocyanidine reductase-encoding SEQ ID NO:14, and thus encompass nucleic acids encoding proteins with 77 amino acid substitutions relative to SEQ ID NO:14. These proteins would have 78.4% identity to SEQ ID NO:14.

The specification does not describe the structural features of a anthocyanine reductase with 80.7% identity to SEQ ID NO:10, or a leucoanthocyanidine reductase with 78.4% identity to SEQ ID NO:14, and thus does not describe the nucleic acids encoding them.

The structural features that distinguish those nucleic acids that modify the levels of chalone synthase, anthocyanine reductase and leucoanthocyanidine reductase in a plant cell from those that do not are not described in the specification.

The other leucoanthocyanidine reductase sequences in the specification, SEQ ID NOs:12 and 16, have greater than 99% identity to SEQ ID NO:14. The specification only described one anthocyanine reductase sequence.

Hence, Applicant has not, in fact, described the constructs the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, Applicant does not appear to have been in possession of the claimed genus at the time this application was filed.

Response to Applicant's arguments

Applicant urges that the claims recite 95% identity (response pg 10).

This is not found persuasive for the reasons above.

6. Claims 83-97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of increasing chalcone synthase, anthocyanine reductase and leucoanthocyanidine reductase levels in a plant by transforming with nucleic acids encoding SEQ ID NO:2, 10 and 14, methods of reducing CHS, BAN and LAR levels in a plant by transforming with nucleic acids encoding SEQ ID NO:2, 10 and 14, full-length complements of those sequences or full-length sequences antisense to those nucleic acids, or 60 bp-long fragments of those nucleic acids, does not reasonably provide enablement for methods of increasing chalcone synthase, anthocyanine reductase and leucoanthocyanidine reductase levels in a plant by transforming with chalcone synthase-, anthocyanine reductase - and leucoanthocyanidine reductase-encoding nucleic acids with 95% identity to any nucleic acid encoding SEQ ID NO:2, 10 and 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Due to Applicant's amendment of the claims, the rejection is modified from the rejection set forth in the Office action mailed 6 January 2011, as applied to claims 65-73, 75-80 and 82. Applicant's arguments filed 18 April 2011 have been fully considered but they are not persuasive.

The claims are broadly drawn to constructs comprising a nucleic acid encoding SEQ ID NOs:2, 4, 6, or 8, a nucleic acid encoding SEQ ID NO:10, and, optionally, a nucleic acid encoding SEQ ID NOs:12, 14 or 16, or a chalcone synthase-encoding nucleic acid that has at least 95% identity to any nucleic acid encoding SEQ ID NOs:2, 4, 6, or 8, an anthocyanine reductase-encoding nucleic acid that has at least 95% identity to any nucleic acid encoding SEQ

ID NO:10, and, optionally, a leucoanthocyanidine reductase-encoding nucleic acid that has at least 95% identity to any nucleic acid encoding SEQ ID NOs:12, 14 or 16. The claims are also drawn to plants comprising the constructs and having modified levels of CHS and BAN and optionally LAR, methods transforming a plant with the constructs to modify tannin biosynthesis, protein binding, metal chelation, antioxidation, UV-light absorption, plant defense to a biotic stress, and forage quality of a plant by disrupting protein foam and/or conferring protection from rumen pasture bloat.

Nucleic acid encoding SEQ ID NO:2, 10 and 14 are the elected sequences; these include SEQ ID NO:1, 9 and 13.

The instant specification fails to provide guidance for how to make chalcone synthase-, anthocyanine reductase- and leucoanthocyanidine reductase-encoding nucleic acids with 95% identity to any nucleic acid encoding SEQ ID NO:2, 10 and 14, respectively.

As discussed above, such nucleic acids encompass those encoding a chalcone synthase with 81.5% identity to SEQ ID NO:2, an anthocyanine reductase with 80.7% identity to SEQ ID NO:10, and a leucoanthocyanidine reductase with 78.4% identity to SEQ ID NO:14, respectively.

The instant specification fails to provide guidance for which amino acids of SEQ ID NO:2, 10 and 14 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain chalcone synthase, anthocyanine reductase and leucoanthocyanidine reductase activities of the encoded proteins. The specification also fails to provide guidance for

which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

The guidance in the specification with respect to making amino acid substitutions in variants is as follows:

The paragraph spanning pg 5-6 defines "functionally active" variants as those that modify flavonoid biosyntheses in a plant and indicates that they can have modification and/or a certain percent identity. Conservative amino acid substitutions are provided as an example of such a modification.

The other leucoanthocyanidine reductase sequences in the specification, SEQ ID NOs:12 and 16, have greater than 99% identity to SEQ ID NO:14. Thus, a comparison of these sequences does not provide guidance for making sequences encoding leucoanthocyanidine reductases with 78.4% identity to SEQ ID NO:14.

The specification provides only one anthocyanine reductase sequence.

Thus, the specification provides little or guidance as to the critical structures of the proteins.

Further, making amino acid substitutions in proteins is unpredictable.

Making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of

those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1).

Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing proteins with up to 155 amino acid substitutions that also have the required enzymatic activities would require undue experimentation.

Thus, extensive teachings are required for making nucleic acids encoding a chalcone synthase with 81.5% identity to SEQ ID NO:2, a anthocyanine reductase with 80.7% identity to SEQ ID NO:10, and a leucoanthocyanidine reductase with 78.4% identity to SEQ ID NO:14, as encompassed by the claimed nucleic acids. These teachings are not provided for by the specification. The specification also fails to overcome the unpredictability of making large numbers of amino acid substitutions in these enzymes as it provides no working examples of proteins with up to 77 amino acid substitutions.

Thus, the instant invention is not enabled throughout the full scope of the claims.

Response to Applicant's arguments

Applicant urges that the claims recite 95% identity (response pg 10).

This is not found persuasive for the reasons above.

7. Claims 98-102 are allowed.

8. In the response filed 18 April 2011 Applicant requests rejoinder of SEQ ID NO:12, 14 and 16. This is agreed, and the restriction between SEQ ID NO:12, 14 and 16 is WITHDRAWN.

Conclusion

9. Applicant's amendment necessitated the modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, Ph.D., whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

June 27, 2011

/Anne R Kubelik/
Primary Examiner, Art Unit 1638